UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,583	04/08/2004	Michael D. Schneider	HO-P02673US1	9750

26271 7590 12/06/2005

FULBRIGHT & JAWORSKI, LLP
1301 MCKINNEY
SUITE 5100
HOUSTON, TX 77010-3095

EXAMINER	
GARVEY, TARA L	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 12/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/820,583	SCHNEIDER ET AL.	
	Examiner	Art Unit	
	Tara L. Garvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/20/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-30 are pending.

Priority

Claims 1-30 are granted priority to provisional application 60/461,095 with a filing date of April 8, 2003.

Information Disclosure Statement

The information disclosure statement submitted May 20, 2005 has been received and all references have been considered except for US 5,118,180. The citation of US 5,118,180 does not appear to be related to the current application.

Claim Objections

Claim 3 is objected to because of the following informalities: Claim 3 is dependent on itself. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8-11,13-24 and 26-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s)

contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The Guidelines for Written Description state "The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (Federal Register, Vol. 66, No. 4, Column 1, page 1105).

In the instant case, the composition that can regulate telomere stability is a critical element of the claimed invention because the composition is the operative embodiment which provides the outcome recited in the claims.

The specification does not describe all the compositions that can regulate telomere stability or all the agents that can modulate TRF2, inhibit HGK2 or modulate Chk2 in all cell types. The specification describes TERT and inhibitors of HGK as modulators of TRF2, but does not describe all the modulators of TRF2. Furthermore, the specification does not describe any specific inhibitors of HGK or modulators of Chk2. The prior art does not offset the lack of description in the specification in that it

does not teach all the compounds that can regulate telomere stability or that specifically modulate TRF2, HGK and Chk2 to regulate telomere stability to increase cell survival. Therefore, there is not a structural and functional relationship provided by the prior art or the specification for one of skill in the art to envision all the compounds that would function as a modulator of TRF2, HGK or Chk2 in the methods of enhancing cell survival and of treating a subject suffering from cardiovascular disease by administering a composition that regulates telomere stability.

Although the application describes methods which might be used to identify compounds that can modulate signaling molecules involved in telomere stability, an adequate written description of an agent requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the agent itself. It is not sufficient to define a compound solely by its principal biological property, i.e. it modulates TFF2, inhibits HGK or modulates Chk2, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any compound with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming a method of using any agent that achieves a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Claims 1-6 and 8-30 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administration of TERT to a cell *in vitro*, does not reasonably provide enablement for administration of any composition that regulates telomere stability *in vitro* and *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art, relative skill in the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claim, with the most relevant discussed below.

Nature of the invention: The claims are directed to a method of increasing the survival of a cell such as a cardiomyocyte *in vitro* or in a subject by regulating telomere stability and thereby treating a subject suffering from cardiovascular disease. The composition can comprise a modulator of TRF2 such as TERT or an inhibitor of HGK or a modulator of Chk2. The modulators of TRF2 can increase the activity, expression or stability of TFR2, while the modulators of Chk2 can inhibit Chk2 activity, reduce Chk2 expression, increase Chk2 degradation or destabilize Chk2. The compositions can be used to treat various cardiovascular diseases such as coronary artery disease, myocardial infarction, heart failure, ischemic heart disease or angina.

Breadth of the claim: The claims are broad in that the composition is used to treat any cardiovascular disease using a composition that can comprise any composition that regulates telomere stability or in particular any modulator of TRF2 or Chk2.

Guidance in the specification/Existence of a working example: The specification does not show any success in treating a cardiovascular disorder by using a method of gene therapy or protein therapy in which the composition stabilizes telomere stability. The specification has demonstrated the role of TRF2, modulators of TRF2 such as TERT and HGK and Chk2 in telomere stability and apoptosis in cardiomyocytes and in heart disease. The working examples demonstrate the role of these molecules through in vitro studies and in vivo studies with TERT or HGK transgenic mice. The specification has not provided any evidence of the ability to use modulators of TRF2 and Chk2 to treat a subject suffering from any cardiovascular disease or disorder. The specification provides general examples of genetic and protein based therapies and lists various cardiovascular diseases that could be treated by telomere stabilization. In terms of specific modulators to use in the treatment method, the specification only provides TERT as a specific modulator of TRF2 and does not provide any specific inhibitors of HGK or modulators of Chk2. Instead, the specification describes that method are available for the screening of compounds that could potentially modulate TRF2 and Chk2.

Data that describes the roles of TRF2, TERT, HGK and Chk2 in the regulation of cardiomyocyte survival cannot be used to predict what effect modulators of these

molecules will provide when administered as a treatment for cardiovascular disease. The specification does not contain any teachings that address the ability of any composition such as compounds that modulate TRF2 or Chk2 or an expression vector encoding TRF2 to treat a human subject suffering from a cardiovascular disease or even its ability to work *in vivo*. Specifically, the specification has not taught a specific composition, an appropriate tested dose for humans, the amount of gene expression necessary for successful treatment for genetic based therapy, the number of cells to be treated, the number of times the treatment needs to be administered or the most appropriate route of administration. The lack of guidance would require trial and error experimentation to determine these factors.

State of the art/Predictability of the art: The prior art demonstrates that treating a disease by a method of gene therapy or protein therapy was not routine.

In terms of gene therapy, the administration of recombinant nucleic acids involving *in vivo* or *ex vivo* methods had not seen any success despite a great deal of work and resources. Several reviews in the art show that difficulties with vector selection, mode of delivery and persistence of predictable and effective levels of expression of the protein, created technical barriers to the practice of gene therapy methods. Verma et al states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Nature Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed-remain a nagging

problem for the entire field", and that "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Volume 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. (Goodman & Gilman's The Pharmacological Basis of Therapeutics (1996), 9th Edition, Chapter 5, McGraw-Hill, NY) explains, "the delivery of exogenous DNA and its processing by target cells requires the introduction of new pharmakinetic paradigms beyond those that describe the conventional medicines in use today". Eck et al teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell or its secretory fat, once produced. These factors differ dramatically based on the vector used, the protein being produced and the disease being treated (see Eck et al, bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al teaches, in reference to *ex vivo* methods, that weak promoters produce only low levels of therapeutically effective protein, and

that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein be achieved (Verma et al, *supra*, page 240, column 2). Verma et al further warns that, "...the search for such combinations is a case of trial error for a given cell type" (Verma et al, *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al, Human Gene Therapy,1996, Volume 7, pages 1781-1790, see page 1789, column 1, first paragraph). Thus, the art at the time at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect in vivo by expressing a therapeutic gene using any of the expression constructs known in the art was extremely low.

More recently, Rubanyi (Mol. Aspects Med. (2001) 22:113-142) teaches that the problems described above remain unresolved. Rubanyi states, "[a]lthough theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see "3. Technical hurdles to be overcome in the future", beginning on page 116 and continued through page 125). Furthermore, Juengst (British Medical Journal (2003) Volume 326, pages 1410-1411) teaches the unpredictable nature of gene therapy and that a few of the apparent successes actually developed T cell-acute lymphoblastic leukemia due to insertional mutagenesis at or near the LMO-2 gene causing altered

gene expression. Thus, as of the filing date of the instant application, gene therapy was regarded as unsuccessful and unpredictable.

In terms of the clinical use of proteins to treat a disease by delivery at the time of filing of the instant application, the art recognized the lack targeting as an important unanswered question and possible limitation to the use of translocating peptides *in vivo*. Kabouridis (2003) *TRENDS Biotechnol.* 21:498-503 teaches, "a major disadvantage [of using translocating peptides] is lack of targeting specificity. Therefore, for each case, it will be important to establish not only that the PTD-chimera has beneficial effect on diseased cells but also that it has no adverse effects on healthy tissue" (first full paragraph on page 502). Schwarze *et al.* (2000) *Trends Cell Biol.* 10:290-295 concurs with the teachings of Kabouridis, stating, "[a]n effective drug must be active only in the diseased cell. As translocating proteins can readily enter all cell types, specificity must be built into the molecule" (second full paragraph on page 294). Thus, Kabouridis and Schwarze *et al.* clearly teach that the usefulness of any given method of delivering a peptide, polypeptide or protein into a cell in a subject will have to be determined on a case by case basis by empirical experimentation, at least because the effects of an untargeted peptide, polypeptide or protein on the organism as a whole is unpredictable.

Kabouridis goes on to teach additional possible obstacles to using translocating peptides *in vivo* including immunogenicity of the translocating peptide itself or its cargo, which also contribute to the unpredictability of the present method (second full paragraph on page 294). Schwarze *et al.* goes on to teach that basic pharmacological questions of tissue distribution, protein half-life, immunogenicity and modes of delivery

are also important questions that need to be addressed in a quantitative fashion (paragraph bridging pages 294-295). Thus, the teachings of Kabouridis and Schwarze *et al.* indicate that, at the time of filing of the instant application, many basic questions regarding the effective use of translocating peptides *in vivo* remained to be answered. As the instant specification provides no guidance directed to this art-recognized unpredictability, these basic questions will have to be answered through experimentation before the broad scope of the instant claims is enabled.

Quantity of experimentation: The art has demonstrated that a large amount of experimentation has already been performed without demonstrating successful gene therapy or intracellular protein therapy methods for treatment of disease. The skilled artisan would not be able to use the methods in the instant claims to treat a patient suffering from a cardiovascular disease with a composition that regulates telomere stability without a large amount of trial and error experimentation to determine ways to achieve expression levels necessary to be sufficient for a therapeutic effect.

Conclusion: In order to practice the claimed invention, the skilled artisan would not have found sufficient guidance in the specification to achieve effective levels of the expressed protein, to select a proper dose or administration route or to determine other factors for a successful treatment. The prior art did not compensate for the lack of guidance in the specification since the teachings do not recognize any clearly successful gene therapy or intracellular protein therapy methods. The skilled artisan would have had to engage in a large amount of experimentation to practice the claimed invention. In view of the lack of guidance and the large amount of experimentation in an

unpredictable art, it would require undue experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 4-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Oh et al (PNAS (2001) volume 98 (18), pages 10308-10313 as referenced in the IDS submitted on May 20, 2005).

Claims 1, 2 and 4-7 are drawn to a method of enhancing the survival of a cell using a composition that regulates telomere stability.

Oh et al teach delivery of telomerase reverse transcriptase (TERT) to cardiac myocytes using a viral vector, which results in the increased survival of the cells (abstract, page 10308, right column, paragraphs 1-2, page 10309, right column, second full paragraph and page 10311, right column, paragraph 3). Oh et al also teach the forcible expression of TERT in a mouse myocardium through the generation of a transgenic mouse expressing TERT, which resulted in maintenance of telomerase activity in the heart, a delay in myocyte exit from the cell cycle and hypertrophy of cardiac myocytes. These results demonstrate an enhanced survival of a cell that is within a tissue (abstract, page 10208, right column, second full paragraph, page 10309,

left column, third full paragraph). In regard to the cell being under oxidative stress, the cardiac myocytes in cell culture and in the transgenic mouse are continuously exposed to oxidants and therefore absent of a limiting definition in the specification the cells are considered to be under oxidative stress. Thus, Oh et al teach all that is recited in the instant claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tara L Garvey whose telephone number is (571) 272-2917. The examiner can normally be reached on Monday through Friday 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) (http://pair-direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center

(Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tara L Garvey
Examiner
Art Unit 1636

TLG

DANIEL M. SULLIVAN
PATENT EXAMINER